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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,807	07/05/2001	Peng Huang	UTSC:618US	9670

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,807	HUANG ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-35 and 37-52* is/are pending in the application.

4a) Of the above claim(s) *6-11,13,19-24,41-44,46 and 48-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-5,12,14-18,25,27-35,37-40,45 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim 36 has been canceled. Claims 37 and 38 have been amended. Claims 1-35 and 37-52 are pending. Claims 6-11, 13, 19-24, 26, 41-44, 46 and 48-52, remain withdrawn from consideration. Claims 1-5, 12, 14-18, 25, 27-35, 37-40, 45 and 47 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The rejection of claims 1-3, 5, 12, 14-18, 25, 27-35, 37, 39, 40, 45 and 47 under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) in view of Mukhopadhyay et al (U.S. 5,958,892) and the abstract of Barchowsky et al (Toxicology and Applied Pharmacology, 1999, Vol. 159, pp. 65-75) is withdrawn in light of applicants declaration.

The rejection of claims 1-5, 12, 14-18, 15, 27-35, 37-40, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) in view of Mukhopadhyay et al (U.S. 5,958,892) and the abstract of Barchowsky et al as applied to claims 1-3, 5, 12, 14-18, 25, 27-35, 37, 39, 40, 45 and 47 in section 9 above, and further in view of the abstract of Oldham et al (Proceed Amer Assoc Cancer Res, 2000, Vol. 41, page 766, reference C23 of the IDS filed October 16, 2001) is withdrawn in light of applicants declaration.

The rejection of claims 1-3, 5, 12, 14-18, 25, 27-35, 37, 39; 40, 45 and 47 under 35 U.S.C. 103(a) as being unpatentable over Uckun et al (U.S. 6,191,123) in view of Mukhopadhyay et al (U.S. 5,958,892, reference A14 of the IDS filed October 16, 2001) is maintained for reasons of record. Claim 38 is also included with this rejection.

Claim 1 is drawn to a method of killing a cell comprising contacting a cell with a first composition comprising an agent that increases intracellular superoxide, and contacting said cell with a second composition comprising 2-methoxyestradiol. Claim 2 embodies the method of

claim 1 wherein said cell is a cancer cell. Claim 3 specifies that said cancer cell be derived from a solid tumor. Claim 4 embodies the method of claim 1 wherein said cell is a human cell. Claim 12 embodies the method of claim 1, wherein the agent that increases intracellular superoxide comprises an arsenate. Claims 14-16 embody the method of claim 1 wherein the administration of the first composition is concurrent, subsequent, prior to the administration of said second composition, respectively. Claim 17 embodies the method of claim 1 wherein said first and second compositions are combined in a single formulation.

Claim 18 is drawn to a method of treating cancer comprising administering to a host a composition comprising 2-methoxyestradiol and an agent which increases intracellular superoxide. Claim 25 embodies the method of claim 18 wherein the agent that increases intracellular superoxide comprises an arsenate. Claims 28-30 embody the method of claim 18 wherein the administration of the first composition is concurrent, subsequent, prior to the administration of said second composition, respectively. Claim 31 embodies the method of claim 18 wherein said first and second compositions are combined in a pharmaceutically acceptable composition. Claim 32 specifies that the pharmaceutically acceptable composition includes a pharmaceutically acceptable carrier. Claims 33-35 embody the method of claim 31, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, and injection, respectively. Claim 36 embodies the method of claim 18 wherein the host has cancer. Claims 37 and 38 specify a solid tumor and leukemia, respectively. Claim 39 embodies the method of claim 18 wherein the first and second compositions are combined in a single formulation.

Claim 40 is drawn to a composition comprising 2-methoxyestradiol and a second compound which increases intracellular superoxide. Claim 45 specifies that the agent that increases intracellular superoxide comprises an arsenate. Claim 47 embodies the composition of claim 40 wherein said composition is a pharmaceutically acceptable composition.

Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject (claims 11-13) and a method for inducing cytotoxicity in a cell (claims 14-17) comprising administering an composition comprising arsenate. Uckun et al teach pharmaceutical composition comprising arsenates and pharmaceutically acceptable carriers and methods of treatment comprising oral, parenteral and injection administration of said

arsenates (column 5, line 51 to column 6, line 41). Uckun et al teach that the compositions and methods are effective at inducing apoptosis in cancer cells and can be administered to a human patient (column 5, lines 52-54). Uckun et al do not teach the combination of the arsenate compounds with 2-methoxyestradiol, or increasing intracellular superoxide by the administration of the arsenate compounds.

Mukhopadhyay et al teach a method for the treatment of cancer comprising the induction of apoptosis in cancer cells by administration of 2-methoxyestradiol. Mukhopadhyay et al teach the combination of treatment with 2-methoxyestradiol with at least one chemotherapeutic agent (column 20, lines 54-67). Mukhopadhyay et al teach that the cancer cell is derived from a solid tumor (claims 1-7). Mukhopadhyay et al teach the a single composition or pharmaceutical formulation that comprises both agents, or the administration of both agents, in distinct compositions at the same time. Mukhopadhyay et al teach that the treatment with 2-methoxyestradiol may precede or follow the treatment with the chemotherapeutic agent (column 21, lines 5-39), thus fulfilling the specific embodiments of claims 14-17 and 28-32 and 39. Mukhopadhyay et al do not specifically teach the combination of 2-methoxyestradiol with an arsenate agent.

The instant situation is amenable to the type of analysis set forth *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose In order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually In the prior art. Applying the same logic to the instant method and composition claims, given the teaching of the prior art of methods of inducing apoptosis In solid tumor by the administration of 2-methoxyestradiol as taught by Mukhopadhyay et al and the method of inducing apoptosis In a solid tumor by the administration of the arsenate compounds of Uckun et al, it would have been obvious to combine both 2-methoxyestradiol and arsenates for the treatment of solid tumors because the idea of doing so would have logically followed from their having been individually taught In the prior art to be useful as agents for treating tumors by the induction of apoptosis In tumor cells. Furthermore, It would have been *prima facie* obvious to one of ordinary skill In the art at the time the claimed invention was made to combine administration of arsenate with

administration of 2-methoxyestradiol.. One of ordinary skill In the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mukhopadhyay et al on the combination of 2-methoxy estradiol with other chemotherapeutic agents and the teachings of Uckun et al on arsenates as chemotherapeutic agents. Although neither reference teaches that arsenate compounds increase intracellular superoxide levels, there would be motivation to combine both 2-methoxyestradiol and the arsenate compounds taught by Uckun et al for the reasons set forth above. Therefore, the increase In intracellular superoxide levels, although not relied upon to render obvious the combination, would be inherent In combined method.

Claim 38 is drawn to the method of claim 18, wherein said cancer is leukemia. It would also be obvious to combine the teachings of Mukhopadya et al with the teachings of Uckun et al as Uckun et al teach a method of treating breast cancer or leukemia and Mukhopadyay et al teach a broad method of treating cancer which would encompass leukemia (claim 1).

Applicant has submitted a declaration under 37 C.F.R. 1.131 which demonstrates that the invention was reduced to practice prior to June 23, 1999. Applicant states that it is not necessary to antedate all the references in a combination used in a rejection under 103. The examiner finds this a correct analysis. However, it is noted that Uckun et al (U.S. 6,191,123) has priority to March 19, 1999 by virtue of provisional application 60/125,337, and Mukhopadhyay et al has priory to the effective filing date of July 30, 1996. Thus, the declaration provided by the applicant does not antedate the combination of Mukhopadhyay et al and Uckun et al.

Applicant argues that in the event that the declaration proves faulty, there is no motivation to combine the references. Applicant asserts that three basic criteria must be met: there must be some suggestion or motivation in the references themselves or in the knowledge generally available in the art to combine the references; there must be a reasonable expectation of success and the combination of prior art references must teach all the claim limitations. .Applicant alleges that the first criteria, that there must e a suggestion to combine the references, is not met by the instant rejection. This has been considered but not found persuasive. Uckun et al teach a method for treating leukemia or breast cancer comprising the administration of an arsenate to a subject. Thus Uckun et al teach arsenate as a chemotherapeutic agent . Mukhopadhyay et al teach the combination of treatment with 2-methoxyestradiol with at least

one chemotherapeutic agent in a method of treating cancer (column 20, lines 54-67). Thus, Mukhopadhyay et al provides the motivation to combine with methoxyestradiol with arsenate in a method of treating cancer.

Applicant argues that applicants specification provides more than ample evidence of the superiority of the claimed composition because said composition has an enhanced ability to kill cancer cells . applicant refers to page 4, lines 7-10 of the specification where it is stated that "the mechanism based combination of compounds produces a synergistic effect that dramatically increases the tumoricidal and/or anti-neoplastic efficacy of each compound. This has been considered but not found persuasive. On page 46, lines 12-23 the specification discloses that the observed cell killing as a result of the combination of 2-methoxyestradiol and ionizing radiation was greater than expected. However, the instant species under examination is arsenate, not ionizing radiation and on page 47, lines 16-18 the specification teaches that the combined effect of 1-methozyestradiol and arsenate on the CLL cells appears to be additive. Thus applicants arguments regard the superiority of the combination of 2 methoxy estadiol and arsenate are not sufficient to overcome the instant rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
8/11/03